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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/544,146	05/05/2006	Shyam S. Mohapatra	USF-T193XC1	9945

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EXAMINER	
SCHNIZER, RICHARD A	
ART UNIT	PAPER NUMBER
1635	
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06/25/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/544,146	MOHAPATRA ET AL.	
	Examiner	Art Unit	
	Richard Schnizer, Ph. D.	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 April 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *42,45,46 and 51-62* is/are pending in the application.

4a) Of the above claim(s) *1 and 7* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *42,45,46 and 51-62* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *02 August 2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

An amendment was filed on 4/23/08. Claims 1, 7, 8, 10, 11, 16, 17, 22-30, 34, 36, 37, and 48-50 were canceled, and claims 51-62 were added as requested.

Claims 42, 45, 46, and 51-62 are pending and under consideration.

Applicant correctly assumed in the response filed 4/23/08 that the Examiner intended in the Action of 11/21/07 to reject claim 42, and not claim 43, which had already been canceled.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 42, 45, 46, and 51-62 rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods of inhibiting expression of Dengue virus (DV) genes within an isolated mammalian host by administering to the isolated host cell a vector that expresses siRNA that reduces expression of a target DV gene in the isolated host cell by RNA interference, does not reasonably provide enablement for inhibiting expression of Dengue virus (DV) genes within a mammalian animal host by administration to the animal host of a vector that expresses siRNA that reduces expression of a target DV gene in the host by RNA interference. The specification does not enable any person skilled in the art to which it pertains, or with

which it is most nearly connected, to use the invention commensurate in scope with these claims.

The claims have been amended to be drawn to methods of inhibiting expression of Dengue virus (DV) genes within a mammalian host by administration to the host of a vector that expresses siRNA that reduces expression of a target DV gene in the host by RNA interference. This clearly requires delivery of the vector to cells that have been, or will be, infected by DV. The term "host" is interpreted as embracing both mammalian animals and isolated mammalian cells. See the specification at page 13, lines 3-6.

Adelman (2001, 2002, of record) taught that thoracic administration of antisense or siRNA expression vectors in mosquitoes allowed inhibition of DV replication in salivary glands. However, these teachings do not provide enablement for siRNA vector delivery and subsequent inhibition of DV replication in mammals due to the vast differences in size and complexity between the two classes of organisms. Further guidance as to how to achieve delivery of an siRNA vector to the appropriate target cells would be required in order to enable the scope of the claimed invention embracing delivery to cells in an mammal in vivo.

Guidance in the specification as to how to achieve delivery to DV target cells is general. For example, the specification at paragraph 50 indicates that the "vectors of the present invention can be administered to a subject by any route that results in delivery of the genetic material (e.g., polynucleotides) and transcription of the polynucleotides of the gene suppressor cassettes into siRNA molecules. For example, the vectors of the present invention can be administered to a host intravenously (I.V.),

intramuscularly (I.M.), subcutaneously (S.C.), intradermally (I.D.), orally, intranasally, etc."

The specification at pages 29 and 30 teaches that dendritic cells (DC) are regarded as the targets for Dengue virus (DV) infection in mammals (citing Marovich (2001) and Wu 2000, of record)). Each of these papers shows that DV will infect DC in vitro, and provides evidence that DC cells present at a site of infection in vivo stained positively for a DV antigen (see e.g. Marovich at paragraph bridging pages 222 and 223, and Fig 5 on pg 223). However, those of skill in the art appreciate that positive staining of phagocytic cells such as DC does not provide proof of infection of DC in vivo. Jessie et al (J. Inf. Dis. 189: 1411-1418, 2004) at page 1411, paragraph bridging columns 1 and 2, taught that "the mere presence of viral antigens within cells does not necessarily mean that the cells in question support viral replication, since antigens may represent phagocytized, killed virus or sequestered immune complexes in the process of being degraded." Jessie further stated that "[e]vidence from in vitro studies suggested that other cells (e.g., hepatocytes, B and T lymphocytes, endothelial cells, and fibroblasts) could be potential targets for virus infection and replication, but relatively little is known about the involvement of these cells in in vivo infections [12 citations omitted]." Wu indicated that the initial target cell for DV infection had not yet been identified (first sentence of introduction on page 816), and the work of Wu and Marovich does not provide such an identification in view of the later teachings of Jessie. In summary, at the time of the invention, in vivo targets for DV infection and replication had not yet been convincingly identified by those of skill in the art, and the specification

fails to provide further evidence for identification of a target. Thus one of skill in the art relying on the teachings of the specification and the prior art would not know to which cells in a mammal an siRNA vector should be delivered.

It was also apparent from the teachings of the prior art that delivery of gene expression vectors in vivo, and obtaining appropriate expression therefrom, was problematic. At the time the invention was made, successful implementation of gene therapy protocols was not routinely obtainable by those skilled in the art.

Verma et al (Nature 389: 239-242, 1997) taught that "there is still no single outcome that we can point to as a success story (p. 239, col 1). The authors stated further, "Thus far, the problem has been the inability to deliver genes efficiently and to obtain sustained expression" (p.239, col. 3).

Anderson (Nature 392:25-30, 1998) confirmed the unpredictable state of the art, stating that "there is still no conclusive evidence that a gene-therapy protocol has been successful in the treatment of human disease" (p. 25, col. 1) and concluding, "Several major deficiencies still exist including poor delivery systems, both viral and non-viral, and poor gene expression after genes are delivered" (p.30).

More recently, Romano et al (2000) reviewed the general state of gene therapy, and found that the problems relating to gene delivery and expression discussed above persisted. See entire document, especially, last sentence of abstract; last sentence of column 1 on page 20 to column 2, line 6; page 21, column 1, lines 1-9 and 18-21; sentence bridging columns 1 and 2 on page 21; and first sentence of last paragraph on page 21. This idea was echoed by Somia and Verma (2000), who noted that delivery

vehicles still represented the Achilles heel of gene therapy, and that no single vector existed that had all of the attributes of an ideal gene therapy vector. See page 91, column 1, lines 5-13 of first paragraph.

Rosenberg et al (Science 287 :1751, 2000) stated that "[a}t present the ethos of the new field of gene therapy is clearly not working. Since the inception of its clinical trials a decade ago, gene therapy's leading proponents have given the field a positive "spin" that is unusual for most medical research. Yet, despite repeated claims of benefit or even cure, no single unequivocal instance of clinical efficacy exists in the hundreds of gene therapy trials." See first full paragraph.

Caplen (2003) taught out that, "[m]any of the problems associated with developing RNAi as an effective therapeutic are the same as encountered with previous gene therapy approaches. The key issues of delivering nucleic acids to the required tissue and cell type, while ensuring an appropriate level of efficacy with minimum toxicity induced by the vector system…". (pg. 581).

In summary, it is clear that in vivo gene delivery and expression is considered highly experimental area of research at this time, and researchers acknowledge that demonstrable progress to date has fallen short of initial expectations due to inadequate delivery and expression systems.

The specification provides no working example of the claimed invention.

Because the target cells for DV infection were not known at the time of the invention, the specification provides only general guidance as to how to deliver the required expression vector, the state of the art regarding therapeutic gene expression in

vivo shows a high level of unpredictability, and the specification lacks a working example, one of skill in the art could not deliver the required expression vector to the appropriate cells in a mammalian host to inhibit expression of Dengue Virus genes without undue experimentation.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 42, 45, 46, 52, 53, 55, 58, and 59 are rejected under 35 U.S.C. 103(a) as being unpatentable over Raviprakash et al (J. Virol. 69(1):69-74, 1995) in view of Adelman et al (J. Virol. 76(24): 12925-12933, 2002), Tuschl et al (US 7,056,704), and Yu et al (PNAS 99(9): 6047-6052, 2002).

The invention is a method for inhibiting the expression of Dengue virus genes within a mammalian host comprising administering to the host an expression vector comprising a polynucleotide encoding an siRNA that reduces expression of a target Dengue virus gene by RNA interference. The specification at page 15, lines3-6 indicates that “host” embraces isolated host cells.

Raviprakash taught a method of inhibiting expression of DV gene products in mammalian LLCMK/2 cells by microinjection of antisense directed at the 5’ end of the portion of the RNA encoding the structural proteins, and the 3’ end of the virus genome.

Cells were exposed to DV after delivery of antisense. The target regions were 15 bases in length. One oligonucleotide was directed to a target sequence common to all four DV serotypes. See abstract; paragraph bridging pages 69 and 70; first full paragraph on page 70; Fig. 1 on page 70; page 73, column 2, lines 22-26.

Raviprakash did not teach a vector encoding siRNA against DV RNA.

Adelman taught a plasmid vector encoding a inverted repeat siRNA directed against Dengue virus prM RNA, and its use to inhibit DV infection. See abstract. Adelman indicated that expression from a Sindbis vector of RNA with antisense polarity and that of RNA with sense polarity were equally effective to induce resistance to DEN-2 in mosquito cells and adult mosquitoes, noting that virus resistance had many of the characteristics of RNA silencing, including the presence of Dengue virus-specific siRNA.

Tuschl stated that "siRNAs are extraordinarily powerful reagents for mediating gene silencing" and that "siRNAs are effective at concentrations that are several orders of magnitude below the concentrations applied in conventional antisense or ribozyme gene targeting experiments." See column 23, lines 15-20.

Yu taught vectors encoding hairpin siRNAs and their use in mammalian cells. See abstract.

It would have been obvious to one of ordinary skill in the art at the time of the invention to modify the method of Raviprakash by substituting for the antisense oligonucleotides a vector encoding one or more siRNAs. One would have been motivated to do so because Tuschl taught that siRNAs were more efficient than antisense. One would have had a reasonable expectation of success in view of the

teachings of Yu. In so doing, one would have been motivated to use any of the target sequences disclosed by Raviprakash or Adelman. One would have been motivated to include expression cassettes for more than one siRNA in order to increase the level of inhibition achieved.

Accordingly it would have been obvious to one of ordinary skill in the art at the time of the invention to modify the method of Adelman (2001) by delivering to a mosquito host an expression vector designed to transcribe an inverted repeat RNA derived from the genome of Dengue virus, as taught by Adelman (2002). One would have been motivated to do so because Adelman (2002) indicated that such vectors provided a more efficient trigger of RNA interference in mosquito cells than did vectors expressing only sense or antisense RNA. Note that the instant specification at page 11, lines 6-12 defines siRNAs to include hairpin structures, and so the definition is not limited to e.g. 21-23 base pair dsRNA products of Dicer, and so the claim term "siRNA would include the hairpin RNAs of Adelman (2002). In any event expression of the RNAs led to accumulation of siRNAs of 21-25 nucleotides in length (see page 12930, column 2).

It is noted that the combined references teach administration of interfering RNAs prior to challenge with Dengue virus, and not to cells already infected with Dengue virus. It would have been similarly obvious to administer the siRNA vector to cells that had been previously infected because one of ordinary skill could reasonably expect to achieve similar inhibition of virus expression. MPEP 2144.04 states that the selection of any order of performing process steps is prima facie obvious in the absence of new or

unexpected results citing Ex parte Rubin , 128 USPQ 440 (Bd. App. 1959), In re Burhans, 154 F.2d 690, 69 USPQ 330 (CCPA 1946), and In re Gibson, 39 F.2d 975, 5 USPQ 230 (CCPA 1930).

Claim 54 is are rejected under 35 U.S.C. 103(a) as being unpatentable over Raviprakash et al (J. Virol. 69(1):69-74, 1995) in view of Adelman et al (J. Virol. 76(24): 12925-12933, 2002), Tuschl et al (US 7,056,704), and Yu et al (PNAS 99(9): 6047-6052, 2002) as applied to claims 42, 45, 46, 52, 53, 55, 58, and 59 above, and further in view of Adelman et al (Insect Mol. Biol. 10(3): 265-273, 2001).

The teachings of Raviprakash, Adelman (2002), Tuschl, and Yu are summarized above. These references can be combined to render obvious methods of inhibiting DV replication in isolated mammalian host cells by administration of a vector encoding an siRNA directed against DV prM or 3' untranslated regions.

These references do not teach siRNA directed against a non-structural gene.

Adelman (2001) showed that antisense directed against DV NS5 prevented DV replication. See last sentence of page 266 (referring to D1GDDAs and D3GDDAs); Fig. 1C on page 267 which shows that D1GDDAs and D3GDDAs are antisense sequences directed against NS5; and Table 1 on page 268 which shows that D1GDDAs and D3GDDAs inhibited DV replication.

It would been obvious to one of ordinary skill in the art at the time of the invention to target NS5 with an siRNA because Adelman (2001) showed that DV replication could

be inhibited by antisense against NS5, and because Tuschl taught that siRNAs were more efficient than antisense.

Claim 57 is are rejected under 35 U.S.C. 103(a) as being unpatentable over Raviprakash et al (J. Virol. 69(1):69-74, 1995) in view of Adelman et al (J. Virol. 76(24): 12925-12933, 2002), Tuschl et al (US 7,056,704), and Yu et al (PNAS 99(9): 6047-6052, 2002) as applied to claims 42, 45, 46, 52, 53, 55, 58, and 59 above, and further in view of Yu et al (US 6852528).

The teachings of Raviprakash, Adelman (2002), Tuschl, and Yu are summarized above. These references can be combined to render obvious methods of inhibiting DV replication in isolated mammalian host cells by administration of a vector encoding an siRNA directed against DV prM or 3' untranslated regions.

These references do not teach a vector conjugated with chitosan.

However, one of ordinary skill appreciates that there is a wide variety of gene delivery techniques which one may employ interchangeably as a matter of design choice. Among these are microinjection (the method used by Raviprakash), lipofection (used by Adelman 2002 and Yu (2002). Yu ('528) also taught that a variety of methods could be used to deliver nucleic acids to cells including microparticle formation with polycations such as chitosan-based compounds, as well as liposome-mediated transfection and microinjection. See column 22, lines 17-44; column 23, lines 30-47; and column 31, lines 22-38. It would have been obvious to one of ordinary skill in the

art to select any of these commonly used transfection techniques, as they were all well recognized in the art as exchangeable alternatives.

Claims 61 and 62 are rejected under 35 U.S.C. 103(a) as being unpatentable over Raviprakash et al (J. Virol. 69(1):69-74, 1995) in view of Adelman et al (J. Virol. 76(24): 12925-12933, 2002), Tuschl et al (US 7,056,704), and Yu et al (PNAS 99(9): 6047-6052, 2002) as applied to claims 42, 45, 46, 52, 53, 55, 58, and 59 above, and further in view of Kumar et al (US 7067633).

The teachings of Raviprakash, Adelman (2002), Tuschl, and Yu are summarized above. These references can be combined to render obvious methods of inhibiting DV replication in isolated mammalian host cells by administration of a vector encoding an siRNA directed against DV prM or 3' untranslated regions.

These references do not teach a vector comprising a tissue-specific or inducible promoter.

One of ordinary skill in the art recognizes that particular promoters are selected as a matter of design choice. Inducible and tissue-specific promoters allow one to control the expression of a given construct either through the type of cell used or through the presence or absence of an inducer. For example, Kumar taught that it is important to employ a promoter and/or enhancer that effectively directs the expression of the DNA segment in the cell type, organelle, and organism chosen for expression. Those of skill in the art of molecular biology generally know the use of promoters enhancers, and cell type combinations for protein expression. Various promoters

employed may be constitutive, tissue specific, inducible and/or useful under the appropriate conditions to direct high level expression of the introduced DNA segment. It would have been obvious to one of ordinary skill in the art to select any of these commonly used promoters based on the need to control expression as a matter of design choice.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner(s) should be directed to Richard Schnizer, whose telephone number is 571-272-0762. The examiner can normally be reached Monday through Friday between the hours of 6:00 AM and 3:30. The examiner is off on alternate Fridays, but is sometimes in the office anyway.

If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, James (Doug) Schultz, can be reached at (571) 272-0763. The official central fax number is 571-273-8300. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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/Richard Schnizer, Ph. D./
Primary Examiner, Art Unit 1635